Remarks

Claims 1-21 and 24-28 were previously pending in the subject application. By this Amendment, claims 1, 4-21, 24 and 28 have been withdrawn, claims 2 and 25 have been amended, and claim 27 has been cancelled. No new matter has been added by these amendments. Accordingly, claims 2, 3, 25 and 28 remain before the Examiner for consideration.

The amendments to the claims have been made in an effort to lend greater clarity to the claimed subject matter and to expedite prosecution. These amendments should not be taken to indicate the applicants' agreement with, or acquiescence to, the rejections of record. Favorable consideration of the claims now presented, in view of the remarks and amendments set forth herein, is earnestly solicited.

Initially, the Drawings and Specification have been objected to. Attached to this Amendment is a replacement Figure 2 that shows the SEQ ID NO identifiers. The applicants have further amended the "Abstract of the Disclosure."

Claim 2 has been objected to as depending from a non- elected claim. By this Amendment, the applicants have amended claim 2 to make it an independent claim, thereby rendering moot this objection.

Claims 2 and 3 have been rejected under 35 U.S.C. §101 as being directed to non-statutory subject matter. In accordance with the Examiner's suggestion, by this Amendment the applicants have amended claim 2 to recite that the claimed protein is "isolated." The applicants appreciate the Examiner's helpful input and respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. §101.

Claims 2, 3 and 25-27 have been rejected under 35 U.S.C. §112, second paragraph. In making this rejection the Examiner states that the recitation of "biological activity" renders this claim indefinite. In accordance with the Examiner's comments, the applicants have now amended claim 2 to specifically refer to tryptophan hydroxylase activity. In view of this amendment, the applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. §112, second paragraph.

Claims 2, 3 and 25-27 have been rejected under 35 U.S.C. §112, second paragraph. The applicants respectfully traverse this ground for rejection to the extent that it might be applied to the claims now presented for examination. In this regard, please note that claim 2 has been amended herein to delete the word "significantly." In view of this amendment, the applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. §112, second paragraph.

Claims 2, 3 and 25-27 have been rejected under 35 U.S.C. §112, second paragraph. The applicants respectfully traverse this ground for rejection to the extent that it might be applied to the claims now presented for examination. In this regard, please note that claim 2 has been amended herein to delete the phrase "in particular." In view of this amendment, the applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. §112, second paragraph.

Claim 27 has been rejected under 35 U.S.C. §112, second paragraph. Please note that claim 27 has been cancelled herein thereby rendering moot this ground for rejection.

Claims 25-27 have been rejected under 35 U.S.C. §112, first paragraph. The applicants respectfully traverse this ground for rejection because the applicants' disclosure provides clear evidence that the applicants were in possession of the subject invention at the time of filing their application.

In making this rejection, the examiner focuses on the recitation, in claim 25, of "at least one additional protein for the regulation of the serotonin metabolism" and, in claim 26, of the additional protein being "a peripheral tryptophase hydroxylase." However, the cases cited by the Examiner in making this rejection are inapposite. In the current case (unlike the cited cases) the point of novelty of the invention is the new use for the claimed protein. Having identified this new use, the inventors also envisioned the use of this protein with other proteins for regulating serotonin metabolism. These other proteins are not being claimed; rather it is merely their use in combination with the protein of the subject invention that is being claimed. Such other proteins would be known to, and readily envisioned by, those skilled in the art having the benefit of the current disclosure.

An analogous situation would be a claim to the use of a new chemotherapy agent in combination with an analgesic. Surely, an applicant making such a claim would not be required to disclose multiple examples of analgesics in order to meet the written description requirement.

Recent court decisions have made it clear that compliance with the written description requirement does not require the type of disclosure that has been set forth as necessary in the outstanding Office Action. See, for example, Capon v. Eshhar, 418 F.3d 1349, 1357, 76 USPQ2d 1078, 1084 (Fed. Cir. 2005).

Because the applicants were in full possession of the claimed invention at the time of filing, the applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. §112, first paragraph.

Claims 2 and 25-27 have been rejected under 35 U.S.C. §112, first paragraph. The applicants respectfully traverse this ground for rejection to the extent that it might be applied to the claims now presented for examination because a person skilled in the art could readily, and without undue experimentation practice the full scope of the invention as now claimed.

Please note that the applicants have amended claim 2 herein to recite 90% homology to the exemplified sequence. Support for this amendment can be found at, for example, page 7, first full paragraph of the specification as filed. Given the high level of skill in this art, as well as the guidance provided in the applicants' specification, a person skilled in the art could readily practice the subject invention with closely-related sequences as now claimed.

Accordingly, the applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. §112, first paragraph.

Claims 2 and 3 have been rejected under 35 U.S.C. §102(b) as being anticipated by Yu *et al.* (WO/2002/97039). The applicants respectfully traverse this ground for rejection because the Yu *et al.* reference does not disclose each and every element of the applicants' claimed invention.

It is a basic premise of the Patent Law that, to anticipate, a single reference must, within its four corners, disclose all of the limitations of the claimed invention. In *Lindemann v. American Hoist and Derrick Co.*, 221 USPQ 481 (Fed. Cir. 1984), the court stated:

> Anticipation requires the presence in a single prior art reference, disclosure of each and every element of the claimed invention, arranged as in the claim. *Connell v. Sears Roebuck and Co.*, 722 F.2d 1542, 220 USPQ 193 (Fed. Cir. 1983); *SSIH Equip. S.A. v. USITC*, 718 F.2d 365, 216 USPQ 678 (Fed. Cir. 1983). In deciding the issue of anticipation, the [examiner] must identify the elements of the claims, determine their meaning in light of the specification and prosecution history, and

> identify corresponding elements disclosed in the allegedly anticipating reference. *SSIII, supra*; *Kalman [v. Kimberly-Clarke*, 713 F.2d 760, 218 USPQ 781 (Fed. Cir. 1983)] (emphasis added). 221 USPQ at 485.

WO 2002/97039 merely discloses that the proteins of WO 2002/97039 "share structural similarity with animal hydroxylases, and particularly tryptophan hydroxylases, which are involved in a rate-limiting step in the biosynthesis of a number of neurologically active compounds, including, but not limited to, DOPA, serotonin and melatonin" (page 2, lines 1 – 5).

WO 2002/97039 does not disclose any biological data verifying the function of the proteins of WO 2002/97039. Thus, neither the nucleic acid sequence depicted in SEQ ID No. 1 nor the polypeptide according to SEQ ID No. 2 of WO 2002/97039 are biologically validated. The assumption of the activity of the polypetide according to SEQ ID No. 2 is solely based on a structural similarity of the protein with animal tryptophane hydroxylases (*in silico*). More importantly, in addition, it is nowhere stated that the polypeptide depicted in SEQ ID No. 2 functions as a neuronal tryptophane hydroxylase (snTPH).

The applicants respectfully point out that for a claim to be anticipated under the principles of inherency, the subject of a single prior art reference must necessarily function in accordance with the limitations of the process or method claimed. *In re King*, 801 F2d 1324, 1326, 231 USPQ 136, 138 (Fed. Cir. 1986). Further,

> the doctrine of inherency is available only when the prior inherent event can be established as a certainty. That an event may result from a given set of circumstances is not sufficient to establish anticipation. . . . A prior inherent event cannot be established based on speculation, or where a doubt exists (emphasis added). *Ethyl Molded Product Co. v. Betts Package Inc.*, 9 USPQ 2d 1001, 1032-33 (E.D. KY 1988).

The cited reference does not disclose with any certainty that the proteins disclosed therein would, in fact, have the activity claimed by the current applicant. The present application teaches that serotonin is independently synthesised by two different tryptophane hydroxylase isoenzymes in the peripheral tissues and in the neurones. The inventors of the present invention have succeeded in providing nucleic acid molecules encoding a protein with the enzymatic activity of a neuronal tryptophane hydroxylase (snTPH).

The physiological effects of a loss of 5-HT-synthesis were investigated through the generation of mice with a genetic deficiency for TPH. Although a lethal phenotype of this genetic manipulation was expected, as it was determined for animals with a deficiency for TH (Q.Y. Zhou, C.J. Quaife, R.D. Palmiter, Nature 374, 640 (1995)), surprisingly viable homozygous TPH-knock out-mice (TPH(-/-)) were generated. These mice lack 5-HT in the periphery. Further, it was possible to determine that the mode of action of 5-HT in primary haemostasis is based on a release of Von-Willebrand-Factor (vWf). Completely unexpected, there was only a slight diminution of stable 5-HT amounts in the classic serotonergic brain regions of TPH(-/-) mice, leading to the identification of a TPH-isoform, which is exclusively expressed in neurones.

A prior art document considered to be relevant in the analysis of novelty must be enabling. WO 2002/97039 does not provide an enabling disclosure that SEQ ID No.2 is a specific neuronal isoform of tryptophane hydroxylase. The cited document does not teach or suggest this discovery. Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 USC §106(b) based on the Yu *et al.* reference.

Claims 25-27 have been rejected under 35 U.S.C. §103(a) as being obvious over Yu *et al.* (WO 2002/97039) as applied to claims 2-3 above and in view of Wang *et al.* (J. Neurochem. 1998) and Veenestra-VanderWeele *et al.* (Mol. Interv. 2003, 72-5, 50 Review). The applicants respectfully traverse this ground for rejection because the cited references, either taken alone or in combination, do not disclose or suggest the applicants' invention as claimed.

The shortcomings of the primary Yu *et al.* reference with respect to the current invention have been discussed above in detail. The secondary references cited in support of this obviousness rejection do not cure or even address the aforementioned deficiencies of the primary reference.

The protein depicted in SEQ ID No.2 of the present invention has been identified as a specifically neuronal isoform of tryptophane hydroxylase. In contrast, the protein according to SEQ ID No.2 of WO 2002/97039 is only *assumed* to have a general tryptophane hydroxylase activity, wherein there is no distinction between peripheral and neuronal tryptophane hydroxylase activity. Thus, WO 2002/97039 fails to disclose that the protein depicted in SEQ ID No.2 of WO 2002/97039

is a specifically neuronal isoform of tryptophane hydroxylase. Without this knowledge there would be no reason to propose the combination therapeutic composition as set forth in claim 25.

It has been well established in the patent law that the mere fact that the purported prior art could have been modified or applied in some manner to yield an applicant's invention does not make the modification or application obvious unless "there was an apparent reason to combine the known elements in the fashion claimed" by the applicant. *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___ (2007). Furthermore, an applicant's invention is not "proved obvious merely by demonstrating that each of its elements was, independently, known in the (purported) prior art." *Id.*

An assertion of obviousness without the required suggestion or expectation of success in the prior art is tantamount to using the applicant's disclosure to reconstruct the prior art to arrive at the subject invention. Hindsight reconstruction of the prior art cannot support a §103 rejection, as was specifically recognized by the CCPA in *In re Sponnoble*, 56 CCPA 823, 160 USPQ 237,243 (1969). The cited references, either alone or in combination, do not provide a suggestion of the claimed invention and, certainly, no expectation of success. Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) based on Yu *et al.* in view of Wong *et al.* and Veenestra-VanderWeele *et al.*

In view of the foregoing remarks and the amendment above, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

The applicants also invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

David Saliwanchik

David R. Saliwanchik
Patent Attorney
Registration No. 31,794
Phone: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

DRS/la

Attachments: Replacement Figure 2
Replacement page 35 (Abstract)